

AperTO - Archivio Istituzionale Open Access dell'Università di Torino

The IFI16 restriction factor cooperates with HCMV pUL83 to down-regulate UL54 gene expression and viral DNA synthesis

This is the author's manuscript

Original Citation:

Availability:

This version is available <http://hdl.handle.net/2318/1526696> since 2016-11-28T09:49:42Z

Published version:

DOI:10.1016/j.cyto.2015.08.067

Terms of use:

Open Access

Anyone can freely access the full text of works made available as "Open Access". Works made available under a Creative Commons license can be used according to the terms and conditions of said license. Use of all other works requires consent of the right holder (author or publisher) if not exempted from copyright protection by the applicable law.

(Article begins on next page)

The IFI16 restriction factor cooperates with HCMV pUL83 to down-regulate UL54 gene expression and viral DNA synthesis

Matteo Biolatti¹, Sara Pautasso¹, Valentina Dell'Oste¹, Marco De Andrea^{1,2}, Jens von Einem³, Bodo Plachter⁴, Manfred Marschall⁵, Marisa Gariglio², Santo Landolfo¹

¹University of Turin, Turin, Italy; ²University of Piemonte Orientale "A. Avogadro", Novara, Italy;

³University Hospital Ulm, Ulm, Germany; ⁴University Medical Center of the Johannes Gutenberg, Mainz, Germany; ⁵University of Erlangen-Nürnberg, Erlangen, Germany

During the early phase of human cytomegalovirus (HCMV) infection, the Interferon- γ -Inducible factor 16 (IFI16) behaves as a pattern recognition receptor (PRR) sensing viral DNA and triggering antiviral cytokine release. Later on, it restricts virus replication by down-regulating expression of viral genes committed to DNA synthesis including UL54 and UL44. These activities are modulated by viral proteins including pUL83, a tegument protein involved in viral evasion. Here, we demonstrate that pUL83 interacts with IFI16 relieving its inhibitory activity on UL54 gene transcription. We also establish that, starting from 48 h post-infection, IFI16 is stabilized and protected from degradation by pUL83 as observed infecting human foreskin fibroblasts with the wild type HCMV strain (v65Rev) or the v65Stop lacking pUL83 expression. Upon infection with an HCMV mutant virus (RV-VM1) expressing a pUL83 lacking the nuclear egression signal (NES), IFI16 is retained in the nucleus and does not migrate into the cytoplasm. Interestingly, accumulation of nuclear pUL83 prevents the formation of discrete puncta and dissipates aggregation of IFI16 filaments. We observe that IFI16 shows an half-life of less than 1 h in the absence of pUL83 compared with 2 h in the presence of pUL83 demonstrating that IFI16 is less stable in the absence of pUL83. Consistent with this, we observe restoration of IFI16 protein in v65Stop-infected cells compared to v65Rev-infected cells in presence of the proteasome inhibitor MG132. Our results demonstrate a novel role for the pUL83 protein that stabilizes and protects IFI16 from proteasome degradation during HCMV infection and modulates suppression of UL54 gene activity